REMARKS

Claims 1-138 were pending in this application and subjected to a restriction requirement by the Examiner. Claims 2, 32-35, 45, 67, 90, and 96, and 101-132 were withdrawn by the Examiner and are cancelled without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claims in subsequent applications. Claims 1, 3-31, 36-89, 91-95, 97-100, and 133-138 were rejected. Claims 1, 3, 4, 14, 20, 27, 29, 39, 42, 48, 49, 55, 57, 64, 68-70, 74, 76-78, 80-85, 88-92, 95, 96, 98, and 99 are amended herein. Support for the amendments can be found throughout the specification. In particular, support for the amendments can be found at page 7, lines 8-9 (synthetic zinc finger proteins); at page 4, lines 25-26 (hexadactyl zinc finger protein); and at page 28, line 29 to page 30, line 10 (mutations at one or more base-contacting positions). It is believed that no new matter has been added. Claims 9-10, 12, 45, 67, and 86-87 are hereby canceled as these claims are believed to be redundant in view of the presently amended claims. Applicants cancel these claims without prejudice and reserve the right to prosecute the subject matter of the canceled claims in subsequent applications. No claim has been allowed. Claims 1, 3-8, 11, 13-31, 36-44, 46-66, 68-85, 88-89, 91-95, 97-100, and 133-138 are currently pending.

Formal Matters

Applicants gratefully acknowledge the rejoining of Groups II and IV and hereby cancel the nonelected claims 2, 32-35, 90, and 96, and 101-132.

The status of the nonprovisional parent application Serial No. 09/620,897 has been updated to reflect its conversion to Serial No. 60/327,552.

A new declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application and other priority applications is submitted herein for each inventor. *See* Exhibits A-D.

Applicants gratefully acknowledge the approval of the drawings by the Examiner.

The Office objected to claim 98 because a plant generated from a plant is unclear. The Office also objected to claim 57, stating that "culturing is in planta" is unclear. Claims 57 and 98 have been amended to clarify the language cited by the Office.

In view of these remarks and amendments, Applicants respectfully request the withdrawal of the objections.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 3-31, 36-69, 83-84, and 133-138 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Office asserts that claims 1 and 4 are indefinite in the recitation of "providing plants cells with a zinc finger protein" and "providing an expression system for a zinc finger protein" as it is unclear how the zinc finger protein resulted in the plant. The Office asserts that it is unclear how the nucleotide sequence encoding the zinc finger protein resulted in the plant. According to the Office, the recitation of a "small molecule" (claim 16), a "taste molecule" (claim 25), a "bad taste molecule" (claim 26), "a metabolic pathway that is heterologous to a plant" (claim 27), "metabolic pathway enhances an input or output trait in plant or seed" (claim 28), and "derived" (claims 133-134, 136 and 138). Claim 49 is allegedly indefinite because it is unclear how plants cells can constitute all the cells of an intact plant. Claims 83 and 84 are allegedly indefinite because claim 76 does not recite a first promoter. Applicants traverse these rejections.

Claims 1, 3, and 4 are amended herein to more particularly point out and distinctly claim a method to stably modulate the expression of a target gene in a transgenic plant cell by introducing into the plant cell a zinc finger protein and the expression system for the zinc finger protein.

Applicants respectfully submit that the recitation of a "small molecule" is not indefinite. The term "small molecule" is defined in the specification at page 25, lines 1-6. Specifically, the specification states:

> As used herein, "small molecule" refers to a molecule that, without forming homo-aggregates or without attaching to a macromolecule or adjuvant, is

> incapable of generating an antibody that specifically binds to the small molecule. Preferably, the small molecule has a molecular weight that is about or less than 10,000 daltons. More preferably, the small molecule has a molecular weight that is about or less than 5,000 dalton.

The above definition clearly definition the metes and bounds of this term, and therefore this recitation is not indefinite.

Applicants respectfully submit that the recitation of a "taste molecule" and a "bad taste molecule" is not indefinite. As stated in the specification, if a term is not defined, it is to have the same meaning as is commonly understood by one of ordinary skill in the art. "Taste" is defined as "the sense that distinguishes sweet, sour, salty, or bitter qualities produced by or as if by a substance in contact with taste buds on the tongue." *See* Exhibit E (THE AMERICAN HERITAGE COLLEGE DICTIONARY 1411 (4th Ed. 2002)). Likewise, the term "bad taste molecule" is to have the same meaning as is commonly understood by one of ordinary skill in the art as "bad" modifies "taste molecule" is a way easily understood by the artisan of ordinary skill. Moreover, Applicants note that these terms describe the metabolic pathway modulated by the claimed zinc finger protein construct. Therefore, these terms described the metabolic pathway through which taste is processed or perceived via any taste molecule.

Claim 27 is amended herein to clarify the modulated protein expression is in a metabolic pathway heterologous to a plant cell. Applicants note that the claim language contemplates the modification of a plant cell with families of transgenes heterologous to the plant cell. Constructs can be designed such that a family of transgenes can be regulated using similar or identical targets for the ZFP portion of the effector protein. *See, e.g.*, the specification, at page 48, lines 21-27. As the specification clearly discloses such a strategy, the term "a metabolic pathway that is heterologous to a plant" is sufficiently definite.

Claim 28 is not indefinite because the terms "input trait" and "output trait" are recognized terms of art in the field of plant biotechnology. *See e.g.*, Exhibit F. The term "input trait" refers to a trait that helps producers by lowering the cost of production, improving crop yields, and reducing the level of chemicals required for the control of insects, diseases, and weeds. The

term "output trait" refers to a trait that helps consumers by enhancing the quality of the food and fiber products they use. Because these terms are recognized terms of art in the relevant field, *i.e.*, plant biotechnology, they are sufficiently definite in view of the specification being directed to methods to recombinantly modify plants.

Claim 49 is amended herein to clarify that the recombinantly modified plant cell in the claim can be in an intact plant or constitute all the cells of an intact plant. The specification discloses various means of transformation of plant cells on, *e.g.*, page 62, line 6 to page 63, line 7. It is apparent to one of ordinary skill in the art that a transformed plant cell can be grown into an intact plant, and thus have the transformed cell constitute the whole intact plant.

Claim 76 is amended herein to clarify that the ZFP gene is controlled by a first promoter in the claimed expression system, and in some embodiments (*e.g.*, claims 83 and 84) a second promoter can control the ZFP gene expression.

The term "derived" in claim 133 is specifically defined in instant specification at page 17, lines 5-8, where it states:

> As used herein, "framework (or backbone) derived from a naturally occurring zinc finger protein" means that the protein or peptide sequence within the naturally occurring zinc finger protein that is involved in non-sequence specific binding with a target nucleotide sequence is not substantially changed from its natural sequence.

In view of this definition, Applicants believe that one of ordinary skill in the art would understand that the derived product contains a framework from the ZFPs specified in the claims. Therefore, in view of the disclosure in the specification, the term "derived" is sufficiently specific.

In view of the above comments and amendments, Applicants request the withdrawal of these rejections.

Rejection Under 35 U.S.C. § 112, First Paragraph - Enablement

Claims 1, 3-30, 36-39, 91-95, 97-100, and 133-138 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to reasonably provide enablement for the pending claims. According to the action, any method to modulate the expression of any target gene with any zinc finger protein capable of binding to said target gene in plant cells, any method of providing plant cells with any zinc finger protein, a method that modulates expression of a target gene encoding a protein that controls a metabolic pathway in a plant cell, or a method that employs a framework derived from a zinc finger protein that is known in the prior art as of the filing date of this application. Claims 31 and 76-89, 91-95, and 97-98 are rejected under 35 U.S.C. § 112, first paragraph as alleged failing to reasonably provide enablement for a method modulating gene expression of a target gene in a plant cell by expressing a zinc finger protein, wherein the method is used for treating a disorder associated with an abnormal expression of the target or a transgenic plant. The Action asserts that the specification does not teach the agronomic benefit or the use of such a transgenic plant. Applicants respectfully traverse this rejection.

Applicants highlight the presently claimed methods are directed to the modulation of gene expression using synthetic zinc finger proteins with defined characteristics that include stable expression in a plant cell, binding specificity for a target sequence of 18bp, and six fingers (*i.e.*, hexadactyl) where at least one zinc finger has a mutation at one or more of the base-containing positions. The claimed methods are not directed to the use of any zinc finger protein. Therefore, for reasons discussed *infra*, the claimed methods are reasonably enabled by the instant specification.

1. The instant specification provides reasonable enablement for the claimed methods.

Applicants respectfully submit that the instant disclosure fully enables the presently claimed methods employing the claimed genus of synthetic ZFPs. First, the specification discloses sufficient guidance for one of skill in the art to make and use the claimed methods.

More particularly, the specification details the construction of novel, synthetic ZFPs (*e.g.*, page 31, lines 3-10); useful linkers (*e.g.*, page 31, lines 25-30); useful ZFP framework regions, (*e.g.*, page 32, lines 4-25); protein purification and characterization protocols (*e.g.*, page 33, line 7 to page 34, line 17); useful effector domains for fusion with the ZFPs (*e.g.*, page 38, line 4 to page 43, line 1); desirable target genes and nucleotide sequences (*e.g.*, page 43, line 3 to page 45, line 29); method of selecting the target sequences (*e.g.*, page 46, line 1 to page 47, line 5); guidance for expression in plants including transformation techniques, vectors, methods for improved expression, useful promoters and expression constructs for ZFPs (*e.g.*, page 47, line 8 to page 59, line 9; page 62, line 6 to page 63, line 27); methods for identifying and isolating promoters for targeting by ZFPs (*e.g.*, page 59, line 10 to page 62, line 5); growing of plants from transformed plant cells (*e.g.*, page 63, line 28 - page 64, line 12; page 65, line 19 to page 67, line 9); as well as guidance as to what proteins and metabolic pathways are desirable to target with ZFP modulation (*e.g.*, page 64, line 13 to page 65, line 16). Second, the specification discloses a number of representative species in the genus of claimed synthetic ZFPs. Specifically, ZFPm1, ZFPm2, ZFPm3, ZFPm4, and ZFPAP3 are disclosed as representative species, as acknowledged by the Office. Third, the specification discloses numerous working examples employing the disclosed representative species. Example 3 successfully employs the described method of identifying potential zinc finger binding sites and designing binding ZFPs. Example 4 details the successful construction of the new ZFPs. Examples 5, 6, and 7 demonstrate the expression and purification of the new ZFP proteins, generation of specific ZFP antibodies, characterization of the DNA binding specificity, and expression in transient expression assays. Examples 8 and 9 show stable expression of one of the representative species, ZFPAP3, in plant cells and include detailed disclosure of methods of transformation, detection of the exogenous ZFP expression, detection of target gene expression and transcription, and the resulting phenotype. Example 11 discloses the construction and function of the maize-specific ZFPs (*i.e.*, ZFPm1, ZFPm2, ZFPm3, and ZFPm4). Finally, the disclosure indicates the applicability of the examples and

other description to the genus as a whole. For example, Applicants state in Example 4: "[t]he following provides details of a typical construction of a zinc finger ... ." See page 87, lines 1-2. Thus, the skilled artisan would expect the claimed genus to be used and made in a similar manner without undue experimentation.

2. The specification provides enabling disclosure for the specific binding to the target sequence in the plant genome.

In rejecting the claimed methods, the Office has apparently taken the position that the efficacy of each and every claimed ZFP must be disclosed in the specification to fulfill the patentability requirements of 35 U.S.C. § 112, first paragraph. However, such is not the legal standard for the enablement requirement. Enablement requires only that representative examples of the claimed genus that are accompanied by a statement applicable to the genus as a whole are ordinarily sufficient for the skilled artisan in view of the level of skill, state of the art, and the information in the specification. *See* MPEP §2164.02 (8th ed. 2001). The specification discloses five representative species that specifically bind a target site within the plant genome as well as a statement indicated that these species are indeed representative of the claimed genus. Applicants specifically disclosed that an 18 bp recognition sequence is desirable in designing ZFP with specific target sequence recognition with the plant genome. *See, e.g.*, the specification, at page 28, lines 22-28. Moreover, Applicants disclosed five representative species binding three distinct sequences in two different genes in the Examples 3-11 as well as evidence that they bind to the expected target region. In other words, the specification provides representative species, the required statement regarding the genus, guidance regarding identification of the remainder of the genus, and evidence that the representative species work as predicted. Thus, while the mechanisms of gene regulation are indeed complex, in light of the guidance provided in the specification, there is sufficient information for one of skill in the art to make and use the claimed methods.

Applicants respectfully submit that Beerli's teachings do not support the Office's argument regarding unpredictability relating to regulating an endogenous gene. First, Beerli's disclosure regarding E3-KRAB and E3-VP64 demonstrate specificity of binding, not the unpredictability of ZFP specificity (as asserted by the Office). Beerli designed E3 to bind ErbB-3, not ErbB-1 or ErbB-2. The absence of regulation of ErbB-1 and ErbB-2 by E3 is interpreted by Beerli as confirming the "exquisite specificity inherent to the zinc finger-based switches described here." *See* Beerli, *et al.* (2000), at page 1498, first paragraph, last sentence. Second, the nonspecificity discussed by Beerli supports the predictability of claimed methods. In the section "Requirements for Imposing Specific Regulation on Endogenous Genes," Beerli discloses several factors that contribute to the specificity (or discrimination) by the ZFP: (1) the size of the bp recognition site, and (2) the binding affinity. Beerli indicates that ZFPs with a 9 bp recognition site and a Kd of 10 nM or more are likely to be nonspecific and may be undesirable. However, the claimed methods employ synthetic ZFPs with an 18 bp recognition site to confer highly specific recognition. Therefore, the disclosure of Beerli confirms that the guidance provided in the specification is adequate to practice the claimed methods.

3. The specification reasonably enables the use of the claimed methods to make and use transgenic plants.

The instant specification discloses and characterizes transgenic plants generated using the claimed methods in Examples 8 and 9. Using the *Agrobacteria* transformation method disclosed in the specification, transgenic plants were created and characterized with regarding to ZFP modulation of the targeted gene expression and the resultant phenotypic changes, *i.e.*, flower structures and fertility. Applicants submit that this direct evidence supports the disclosure as enabling for the making and using of the claimed methods to generate transgenic plants.

4. The specification enables methods to treat abnormal expression of a target gene in plant cells using synthetic ZFPs.

Applicants respectfully submit that the specification provides sufficient guidance for one of ordinary skill in the art to use the claimed methods to treat abnormal expression of a target gene in plant cells using the claimed ZFPs. As disclosed in the Examples, the claimed methods can be employed to repress or activate a specific gene. *See, e.g.*, Example 8. Because abnormal gene expression usually results from the inappropriate activation or repression of an endogenous gene, a method to repress or activate that gene is readily employable to treat such a disorder. Applicants note that the novelty of the claimed methods lies in the method itself, and not in the discovery of any particular plant disease or gene causing a plant disease. Thus, the claimed methods should be readily applicable to any situation where specific gene regulation is appropriate.

5. The specification discloses the agronomic benefit of ZFP transgenic cells and plants.

Contrary to the assertion of the Office, Applicants have expressly disclosed the agronomic benefit of the claimed methods. At page 64, lines 4-12, the specification states:

> The method of the invention is particularly appealing to the plant breeder because it has the effect of providing a dominant trait, which minimizes the level of crossbreeding necessary to develop a phenotypically desirable species which is also commercially valuable. Typically, modification of the plant genome by conventional methods creates heterozygotes where the modified gene is phenotypically recessive. Crossbreeding is required to obtain homozygous forms where the recessive characteristic is found in the phenotype. This crossbreeding is laborious and time consuming. The need for such crossbreeding is eliminated in the case of the present invention which provides an immediate phenotypic effect.

Therefore, the agronomic benefit is clearly disclosed. Nonetheless, Applicants respectfully submit that the agronomic benefit of regulating gene expression is self-evident to one of ordinary skill in the art. It is well recognized that the ability to regulate endogenous and/or exogenous gene expression in a cell permits the enhancement of desirable traits and the elimination of undesirable traits. Such traits are readily identifiable regardless of the cell system.

For these reasons, Applicants respectfully request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph - Written Description

Claims 1, 3-31, 36-89, 91-95, 97-100, 133-138 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking sufficient written description for methods using any and all zinc finger proteins, DNAs encoding them, and any and all target genes in a plant. Applicants traverse this rejection.

Applicants highlight the presently claimed methods are directed to the modulation of gene expression using synthetic zinc finger proteins with defined characteristics that include stable expression in a plant cell, binding specificity for a target sequence of 18bp, and six fingers (*i.e.*, hexadactyl) where at least one zinc finger has a mutation at one or more of the base-containing positions. The claimed methods are not directed to the use of any and all zinc finger protein, DNAs encoding them, and any and all target genes in a plant. Therefore, for reasons discussed *infra*, the instant specification provides sufficient written description.

Applicants respectfully submit that the specification provides sufficient guidance for the presently claimed methods. As stated above, the specification details the construction of novel, synthetic ZFPs (*e.g.*, page 31, lines 3-10); useful linkers (*e.g.*, page 31, lines 25-30); useful ZFP framework regions, (*e.g.*, page 32, lines 4-25); protein purification and characterization protocols (*e.g.*, page 33, line 7 to page 34, line 17); useful effector domain for fusion with the ZFPs (*e.g.*, page 38, line 4 to page 43, line 1); desirable target genes and nucleotide sequences (*e.g.*, page 43, line 3 to page 45, line 29); guidance for expression in plants including transformation techniques, vectors, methods for improved expression, useful promoters and expression constructs for ZFPs (*e.g.*, page 47, line 8 to page 59, line 9; page 62, line 6 to page 63, line 27); methods for identifying and isolating promoters for targeting by ZFPs (*e.g.*, page 59, line 10 to page 62, line 5); growing of plants from transformed plant cells (*e.g.*, page 63, line 28 - page 64, line 12; page 65, line 19 to page 67, line 9); as well as guidance as to what proteins and metabolic pathways are desirable to target with ZFP modulation (*e.g.*, page 64, line 13 to page 65, line 16). In

particular, the specification describes the identification of suitable binding sites for ZFPs. *See, e.g.*, page 46, line 1 to page 47, line 5. The specification discloses five representative species, designed and tested using the guidance in the disclosure, and includes multiple working examples. Thus, one of skill in the art can readily visualize or recognize the identity of the members of the genus.

In view of the reasons discussed, Applicants respectfully request the withdrawal of this rejection.

Rejections Under 35 U.S.C. § 102(b)

Applicants gratefully acknowledge that claims 18, 26-27, 37, 46, 49, 57, 71-72, 79, and 100 are free from the prior art of record.

Claims 1, 3-9, 13-17, 19-20, 22-25, 28-30, 38-39, 44, 47-48, 50-56, 58-60, 67-70, 73-78, 83-84, 88-89, 91-93, 133, and 136-138 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Yanagisawa et al. According to the Action, Yanagisawa teaches a method of controlling the expression of a gene in maize leaf tissues using Dof1 zinc finger proteins. The Office asserts that the expression of the gene regulated by Dof1 in the photosynthesis pathway, thus inherently enhancing the photosynthesis of the plant. Claims 1, 3-7, 9, 17, 19-20, 22, 29-30, 39-41, 44, 47-48, 51-52, 54-56, 67-69, 74-78, 83, 85-86, 89, 91, 93, and 133-138 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by de Pater, et al.. The Office asserts that de Pater teaches a method of activating gene expression in plant cells with ZAP1, a zinc finger protein, thus increasing the transcriptional activity of the target gene. According to the Office, de Pater discloses ZAP-1 as a sequence specific zinc finger protein, implying that ZAP1 can impose transcriptional activation on all target genes with the disclosed optimal sequence in the promoter region. Applicants traverse these rejections.

1. Yanagisawa fails to anticipate the claimed methods.

Yanagisawa does not anticipate the presently claimed methods because each and every element of the claimed methods is not described in the reference. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."). First, Yanagisawa contains no disclosure regarding the stable expression of ZFPs in plant cells. Yanagisawa discloses the expression of ZFPs using only a transient protoplast assay. Stable transformation and transient transfection are distinct processes. Stable transformation requires that (1) the expression construct successfully integrate into the plant genome, a low frequency event in plant cells, and (2) upon integration, the expression construct is expressed, *i.e.*, not subject to silencing by surrounding genomic elements. Therefore, the disclosure of methods using transient transfection does not encompass the instant methods using stable transformation. Second, Yanagisawa does not disclose, teach, or suggest the use of synthetic ZFPs. Yanagisawa discloses Dof ZFPs, a naturally occurring ZFP as well as some cursory disclosure on other naturally occurring ZFPs. Third, Yanagisawa contains no disclosure regarding the size of the nucleotide sequence bound by the Dof ZFP or any desirable mutations in the ZFP. In the absence of a disclosure or teaching regarding stable transformation, the use of synthetic ZFPs, or the use of the specific, synthetic ZFPs claimed, Yanagisawa does not anticipate the claimed methods.

2. de Pater fails to anticipate the claimed methods.

Like Yanagisawa, de Pater fails to teach stable transformation of plant cells with ZFPs, synthetic ZFPs, and ZFPs binding an 18 nucleotide sequence with mutations in one or more base-containing position in at least one zine finger. de Pater discloses only the transient expression of ZFPs in plant cells, and the ZFP disclosed is the naturally-occurring ZAP-1. Therefore, like Yanagisawa, de Pater is not a proper anticipatory reference.

For the reasons discussed above, Applicants respectfully request the withdrawal of these rejections.

Rejections Under 35 U.S.C. § 103(a)

Claims 1, 3-17, 19-20, 21-25, 28-30, 31, 36, 38-45, 47-48, 50-56, 58-60, 67-70, 73-78, 80-89, 91-95, 97-99, and 133-138 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yanagisawa in view of Barbas *et al.* (WO 98/54311). The Office acknowledges that the method in Yanagisawa does not teach the use of non-natural zinc finger proteins to control gene expression in plants. Barbas discloses a method of regulating expression of genes with designed zinc finger proteins derived from wild type proteins known in the art and having specific recognition sites.

Claims 1, 3-9, 17, 19-20, 21-24, 29-30, 31, 36, 38-45, 47-48, 51-52, 54-56, 58-60, 67-70, 73-78, 80-89, 91-94, 97-99, and 133-138 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over de Pater et al., *Nucleic Acids Res.*, 24: 4624-31 (1996), in view of Barbas *et al.* The Office acknowledges that De Pater does not teach a method using non-natural zinc finger proteins to control gene expression in plants. Barbas discloses a method of regulating expression of genes with designed zinc finger proteins derived from wild type proteins known in the art and having specific recognition sites. According to the Office, it would have been obvious to modify the wild type zinc finger proteins taught by de Pater by using the zinc finger protein design and selection methods taught by Barbas.

Claims 1, 3-17, 19-20, 21-25, 28-30, 31, 36, 38-45, 47-48, 50-70, 73-78, 80-89, 91-95, 97-99, and 133-138 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yanagisawa in view of Barbas. The Office acknowledges that Yanagisawa in view of Barbas does not teach the inclusion of a transit peptide in the plant expression vector. The Office asserts that the inclusion of a transit peptide that targets the desired organelle is well known in the prior art.

Claims 1, 3-9, 17, 19-20, 21-24, 29-30, 36, 38-45, 47-48, 51-52, 54-56, 58-60, 61-70, 73-78, 80-89, 91-94, 97-99, and 133-138 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over de Pater in view of Barbas, as applied to claims 1, 3-9, 17, 19-20, 21-24, 27, 29-30, 36-45, 47-48, 51-52, 54-60, 67-70, 73-78, 80-89, 91-94, 97-99, and 133-138 and in further view of Applicants' admitted prior art. The Office acknowledges that de Pater in view of Barbas does not teach the inclusion of a transit peptide in a plant expression vector. According to the Office, the use of a transit peptide was well known in the art.

Applicants traverse these rejections.

The combination of the cited references does not result in the claimed methods because not all features of the claimed methods are taught, disclosed, or suggested. Neither Yanagisawa nor de Pater teach the use of synthetic ZFPs. Barbas does not correct this deficiency. Barbas discloses the modification and mutation of wild-type zinc finger proteins. *See, e.g.*, Barbas, at page 14, lines 15-18, and at page 49, lines 14-16. Barbas does not disclose or suggest the construction of synthetic ZFPs where the ZFP is constructed based on the desired target sequence of interest and not a known, naturally-occurring ZFP. The combination of these reference and the other art cited by the Office do not teach, disclose, or suggest anything about the strategy for identification and synthesis of such designer ZFPs. Thus, the cited references do not teach, much less suggest the presently claimed methods.

Applicants respectfully submit that the mere fact that Yanagisawa or de Pater can be combined or modified with Barbas does not render the combination obvious because the proposed modification would render the disclosure of Yanagisawa and de Pater unsatisfactory for its intended purpose. See MPEP § 2143.01 ("If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." (citations omitted)). Both Yanagisawa and de Pater characterize novel, naturally-occurring ZFPs. There is no teaching or suggestion to modify the ZFPs taught in these references. In fact, since the references are

seeking to characterize and understand the activity of naturally-occurring ZFPs, modifications away from the natural product would defeat the purpose of their study. Thus, such a modification is non-obvious.

Moreover, the combination of references cited by the Office does not provide a reasonable expectation of success. The disclosures of Yanagisawa and de Pater are limited to transient transfection assays. While Barbas discloses a possibility of stable transformation in plants, the examples in Barbas employ only transient transfection of mammalian cells. As discussed *infra*, the stable transformation of bacterial and mammalian cells does not predict effective and stable transformation in plants. The presence of cells walls, distinct recombination events, and generally lower integration frequency render successful plant cell transformation with exogenous constructs distinct from that of other cell types. Thus, the expression of designer ZFPs in Barbas offer no expectation of success for the claimed methods for stable expression of synthetic ZFPs in plant cells.

In the absence of a motivation to combine or a reasonable expectation of success in making such a combination, the cited references do not establish *prima facie* obviousness.

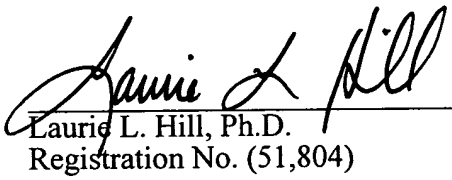
For these reasons, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

Applicants submit that the objections and the rejections under 35 U.S.C. §§ 102, 103, and 112 have been overcome by the above remarks. Early allowance of pending claims 1, 3-8, 11, 13-31, 36-44, 46-66, 68-85, 88-89, 91-95, 97-100, and 133-138 is respectfully requested. If the Examiner thinks a telephonic conference would be helpful, please call the undersigned at (858) 720-7955 at your convenience.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing 278012001420. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: September 22, 2003 By: 

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